Remarks

Following entry of the current amendment, claims 1-15, 17, 20 and 21 are pending. Claims 15 and 17 have been amended to focus on particular embodiments of the invention. Support for the amendments may be found in the specification as originally filed (see, for example, the claims as originally filed).

The Office Action states that the instant application contains multiple groups of inventions, and requires Applicants to elect a single invention from the following:

Group I, claims 1-15, and 17, drawn to compounds and pharmaceutical composition; and

Group II, claims 20-21, drawn to the method of treating various diseases with the compound(s).

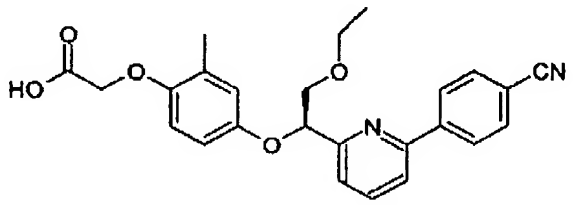
Applicants provisionally elect Group I, with traverse.

The Office Action states that the inventions of Groups I and II are not so linked as to form a single general inventive concept under PCT Rule 13.1. Applicants respectfully disagree with this assertion. MPEP §1850 provides "[i]n applying PCT Rule 13.2 [to national stage applications] examiners should consider for unity of invention all the claims to different categories of invention in the application and permit retention in the same application for searching and/or preliminary examination, claims to the categories which meet the requirements of PCT Rule 13.2." Furthermore, the method for determining unity of invention contained in PCT Rule 13.2 is explained in detail for three particular situations. Relevant to the instant application, MPEP §1850(C) "Combinations of Different Categories of Claims," in pertinent part, states that unity of invention shall be construed as permitting, in particular, the inclusion of the following combination(s) of claims of different categories in the same application:

(A) In addition to an independent claim for a given product, an independent claim for a process and an independent claim for a use of the said product.

Claims 20-21 are in a different category of claims than claims 1-15 and 17 (i.e. "use" claims and "product" claims, respectively). However, MPEP §1850(C) states that unity of invention shall be construed as permitting the inclusion of this type of combination of claims in the same application. Therefore withdrawal of the restriction requirement for election of Group I or Group II is respectfully requested.

The Examiner has required an election of a single species. In response to such election requirement, Applicants provisionally elect with traverse, example 64, also known as [(4-{[(1R)-1-[6-(4-Cyanophenyl)-2-pyridinyl]-2-(ethyloxy)ethyl]oxy}-2-methylphenyl)oxy]acetic acid, and having the structure:



Additionally, Applicants identify claims 1-15, 17, and 20-21, as amended, as claims readable on the elected species.

The Office Action states that the species listed in the instant application do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, the species lack the same or corresponding "special technical feature" that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. Applicants believe this assertion to be improper. As stated in MPEP §1850(D) "Markush Practice," in pertinent part, Rule 13.2

shall be considered to be met when the [chemical] alternatives are of a similar nature. [C]hemical compounds shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) All alternatives have a common property or activity; and

(B)(1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives.

§1850(D) further states a "significant structural element is shared by all of the alternatives" refers to cases where compounds share a common chemical structure which occupies a large portion of their structures, and the structural element may be a single component or a combination of individual components linked together. Applicants submit that compounds of Formula (1) possess the required special technical feature since the components of Formula (1) linked together provide a common structural element, and the alternatives all have the common activity of activating PPARδ. See, for example, Page 142, lines19-20, and Example 18 of Annex B Part 2 of the administrative instructions under the PCT.

The Examiner cites compound GC-1 by Chiellini et al. as evidence that the inventions of Group I and Group II lack contribution over the prior art and do not link the product and method claims into a single general inventive concept, thus lack unity. Applicants respectfully disagree with the Examiner's assertion. Applicants' invention is structurally distinct from compound GC-1 of Chiellini et al. Therefore, Applicants respectfully request the lack of unity objection be withdrawn.

The Office Action states claims 1-5 and 17 are rejected under 35 USC 103(a) as being unpatentable over Chiellini et al., because the prior art compound cited by the examiner and the instant invention are homologues of each other, and because it would have been obvious to one of ordinary skill in

the art to synthesize homologues of the prior art compounds. Applicants respectfully traverse this rejection.

As stated in MPEP 2143 *et seq.*, it is the burden of the Examiner to establish a prima facie case of obviousness, including 1) demonstrating some suggestion or motivation in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference; and 2) show that there is a reasonable expectation of success.

The Examiner states that it would have been obvious to one of ordinary skill in the art to synthesize homologues of the class of compounds disclosed in Chiellini et al. However, the Examiner has failed to demonstrate "some suggestion or motivation" to modify the prior art to arrive at the new claimed invention. Homologues are compounds that form a part of a series, differing from one another by the successive addition of the same chemical moiety, e.g. a -CH2- moiety. For example, ethanol (CH3CH2OH) and n-propanol (CH3CH2CH2OH) represent homologous alcohols.

The close structural similarity of these adjacent homologues gives rise to a presumption that the skilled artisan would expect these compounds to possess similar properties. *See In re Henze*, 181 F.2d 196, 200-01, 85 U.S.P.Q. 261, 264 (C.C.P.A. 1950); partially overruled by *In re Stemniski*, 444 F.2d at 587, 170 U.S.P.Q. at 348 (holding that there is no presumption where no usefulness disclosed for prior art compounds); *In re Wilder*, 563 F.2d 457, 460-461, 195 U.S.P.Q. 426, 430 (C.C.P.A. 1977); *In re Hoke*, 560 F.2d 436, 438, 195 U.S.P.Q. 148, 149 (C.C.P.A. 1977) (considering a branched homolog obvious in view of a linear homolog in the prior art).

Homology, however, should not automatically lead to a conclusion of *prima facie* obviousness. *See In re Elpern*, 326 F.2d 762, 767, 140 U.S.P.Q. 224, 228 (C.C.P.A. 1964) (stating that the greater the difference in the carbon chain, the better the chance to argue against the presumption of obviousness). The facts and holding of *In re Langer*, 465 F.2d 896, 175 U.S.P.Q. 169 (C.C.P.A. 1972), illustrate this proposition.

In *Langer*, appellants found that sterically hindered amines, when added to a catalytic polymerization reaction as a dyeing agent, deactivated the catalyst to a lesser degree than the prior art amines. *Id.* at 897, 175 U.S.P.Q. at 170. The appellants filed a patent application claiming this use of the sterically hindered amines. Because the prior art taught a litany of amines for the same use, including a single, sterically hindered amine homologous to the claimed amines, the PTO rejected the claimed process as obvious. *Id.* at 898, 175 U.S.P.Q. at 171.

On appeal, the court reversed, stating first that § 103 requires analysis of the prior art and claimed subject matter "as a whole." The required analysis of the invention "as a whole,"

> supersedes 'rules' which might emerge from the repeated application of other principles . . . [s]o . . .while this court has found the prior art disclosure of homologues of compounds to render prima facie obvious claims to those compounds, homology should not be automatically equated with prima facie obviousness.

In re Langer, 465 F.2d at 898-99, 175 U.S.P.Q. at 171 (citations omitted).

Determining that the invention as a whole included the use of sterically hindered amines to solve a particular problem, the court found that the isolated presence in the prior art of a hindered amine, outside the scope of the claims, failed to teach or suggest the significance of using the class of sterically hindered amines. Therefore, analyzing the invention as a whole prevented the structural similarity of the homologs from establishing a *prima facie* case of obviousness under the appropriate analysis. *Id.* at 899, 175 U.S.P.Q. at 171. *See also In re Magerlein*, 602 F.2d 366, 372-73, 202 U.S.P.Q. 473, 479 (C.C.P.A. 1979)(considered the invention "as a whole" as including the ability of the claimed intermediate homologs to cause the end product to have an unexpectedly superior property); and *Redox Technologies, Inc. v. Pourreau*, 2004 WL 1947177 (Dept. Comm. A.L.J.)(March 30, 2004)(claims of both parties in interference found obvious. Prior art taught preparation of tert-butyl peroxide from "tert-butyl" reactants, while claims at issue recited preparing di-tert-amyl

peroxide by the reaction of either tert-amyl products. The Board found that one having ordinary skill organic peroxide arts would expect that tert-amyl reactants to have similar properties, and thus react similarly to their tert-butyl homologs.).

Regarding alkylene homologs, *In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A. 1977), represents a case where, without barely more than the structural similarity of the prior art alkylene homologs, the CCPA affirmed the examiner's *prima facie* case. Appellant claimed compositions of adamantane-amine derivatives with a methylene group linking the adamantane moiety to the amine moiety. Appellant's claimed methods of using these compositions for curbing the appetites of animals.

The PTO applied three references against the claims. The compounds in one of the references differed from those claimed by having an ethylene linking group instead of the claimed methylene linking group. The other two references disclosed an adamantane compound linked to other moieties by lower alkylene groups. *In re Shetty*, 566 F.2d at 84, 195 U.S.P.Q. at 755. The prior art taught using the compounds as antiviral and hypoglycemic agents, but made no mention of Appellant's use of curbing the appetite of animals. *Id.* at 83-84, 195 U.S.P.Q. at 754-55. Focusing on the structural similarity between the ethylene group of the first reference and the methylene group of the claims, the PTO held both the composition and method claims obvious over the prior art. *Id.* at 84-85, 195 U.S.P.Q. at 755.

Affirming the obviousness of the composition claims on this basis, the CCPA stated that the difference of a mere methylene group between the claimed compound and the prior art compound was a "minor molecular modification [that] would clearly be obvious to the pharmaceutical chemist." *Id.* at 85-86, 195 U.S.P.Q. at 756. The court further noted the absence of comparative or other evidence demonstrating unexpected properties of the claimed composition. *Id.* at 86, 195 U.S.P.Q. at 756.

The court, however, reversed the PTO finding of obviousness regarding the method claims. The court stated that "prior to appellants' disclosure none of

the adamantane compounds in any of the references . . . suggested a use, much less a dosage, for curbing appetite." *Id.* at 86, 195 U.S.P.Q. at 756-57.

Other cases dealing with alkylene homologs seem to have extended the analysis beyond mere structural similarity. For example, in *Ex parte Goonewardene*, 160 U.S.P.Q. 287 (Bd. Pat. App. 1968), the Board held an insecticide having a methylene group linking two moieties unobvious over a herbicide/fungicide with no linking group. Although characterizing the presence of the claimed methylene bridge as a "significant difference," the Board also focused on the difference in utilities of the compounds. *Id.* at 288. Similarly, the CCPA in *In re Mills*, 281 F.2d 218, 126 U.S.P.Q. 513 (C.C.P.A. 1960), found a methyl sulfate unobvious in view of prior art alkyl sulfates having an alkyl "within the 8 to 12 carbon atom range." *Id.* at 220, 126 U.S.P.Q. at 515. The CCPA considered the homologs too "widely separated" in the number of carbon units, adding that such a homologous relationship "should, therefore, be treated as a chemist would treat it, being nothing more than a fact which must be considered with all other relevant facts before arriving at the conclusion of obviousness." *Id.* at 224, 126 U.S.P.Q. at 518.

Therefore, even though the Examiner states that the prior art compound and the instant compounds are homologues of each other, these facts do not give rise to a prime facie case of obviousness. There still must be "some suggestion or motivation" to modify the prior art to arrive at the new claimed invention, and such motivation must be found in the prior art, not the Applicant's specification.

In order to establish a *prime facie* case of obviousness, the Examiner must also show a reasonable expectation of success. It is well known that the pharmaceutical arts are highly unpredictable. The fact that the prior art compounds are useful as thyroid hormone analogues does not give rise to any presumption or reasonable expectation that the new claimed invention would be useful as PPAR delta activators, and useful for treating diseases or conditions such as dyslipidemia, syndrome X, heart failure, hypercholesterolemia,

cardiovascular disease, obesity, type 2 diabetes mellitus, type 1 diabetes, insulin resistance, hyperlipidemia, anorexia bulimia and anorexia nervosa. Thus, the Examiner has failed to establish a reasonable expectation of success as required by MPEP §2143.

For the reasons stated above, the Examiner has failed to point out where "some suggestion or motivation" exists in the references themselves or the knowledge generally available to one of ordinary skill in the art to modify the reference to arrive at the instant invention. Also, the Examiner has failed to demonstrate a reasonable expectation of success. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness, and the rejection is nothing more than improper hind-site construction of the Applicant's claimed invention. Applicants respectfully request withdrawal of the rejection.

The Office Action states claims 1-5, 10, and 17 are rejected under 35 USC §103(a) as being unpatentable over Fribe et al. because Friebe teaches a small group of compounds within a genus that overlaps in subject matter with the instant genus, and it would have been obvious for one of ordinary skill in the art to easily envision and test the compounds that overlap with the prior art genus of compounds. Applicants respectfully traverse this rejection. As stated in MPEP 2143 *et seq.*, it is the burden of the Examiner to establish a prima facie case of obviousness, including 1) demonstrating some suggestion or motivation in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference; and 2) show that there is a reasonable expectation of success. The Examiner has failed to demonstrate "some suggestion or motivation" to modify the prior art to arrive at the new claimed invention, and has not shown any reasonable expectation for success. MPEP §2144.08(II), citing *Graham v. John Deere*, 383 U.S. 1, 17-18, (1966), requires that to make out a case of obviousness, one must:

(A) determine the scope and contents of the prior art;

(B) ascertain the "differences between the prior art and the claims in issue;

(C) determine the level of ordinary skill in the pertinent art; and

(D) evaluate any evidence of secondary considerations.

MPEP §2144.08(II)(A)(2) provides that in ascertaining the differences between the prior art and the claims in issue, the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed, and specific findings on the similarities and differences between the prior art and instant invention relating to similarity of structure, chemical properties, and utilities, should be made. Further, the court in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1537, 218 USPQ 871, 877 (Fed. Cir. 1983) stated that "the question under 35 USC §103 is not whether the differences [between the claimed invention and the prior art] would have been obvious" but "whether the claimed invention *as a whole* would have been obvious." (emphasis in original). The Examiner states that Friebe et al. teaches the compound as shown in Formula I, where A is alkylene with 1 to 2 carbon atoms, B is an oxygen atom, m is 1, X is a valency bond, Y is a valency bond, Z is halogen, C1-6 alkyl, and R is COOH. The Examiner further states that the patentee teaches a small group of compounds within a genus that overlaps in subject matter with the instant genus, [thus] it would have been obvious for one of ordinary skill in the art to easily envision and test the compounds that overlap with the prior art genus of compounds. In applying the guidance of the court in *Stratoflex*, comparison of the compound cited by the Examiner from Friebe, to the Applicants invention *as a whole*, provides such little overlap, that one skilled in the art would be left without the necessary teachings and motivation to arrive at the instant invention. For example, compare (in pertinent part) the following:

(1) the Friebe compound where the radical Z is halogen or C1-6 alkyl, and bonding of the radical is in the 2-, 3- or 4-position of the pyridine; with

(2) the instant invention wherein R7 is phenyl or a 6-membered heteroaryl group containing 1, 2, or 3 nitrogen atoms wherein the phenyl or heteroayl group is substituted by 1, 2, or 3 moieties selected from the group consisting of halogen, C1-6 alkoxy, C1-6 alkyl, CF3, hydroxyl, or phenyl (which may be optionally substituted by one or more C1-3 alkyl, -OC1-3 alkyl, CN, acetyl, hydroxyl, halogen or CF3).

The required modifications of the compounds in (1) to arrive at the compounds in (2) are substantial. Additionally, the Examiner fails to point out where in the prior art the motivation exists to change the Friebe compounds in (1) to arrive at the instant invention in (2). Therefore, when considering the invention *as a whole*, the instant invention is not obvious when compared to the prior art.

Furthermore, MPEP §2144.08(II)(A)(3)(a) provides that there is no absolute correlation between the size of the prior art genus and a conclusion of obviousness, citing *Baird*, 16 F.3d at 383, 29 USPQ2d at 1552 (observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved"). Also, some motivation to select the claimed species or subgenus must be taught by the prior art. See, for example, *Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215. Although the Examiner states that the patentee teaches a small group of compounds within [the] genus that overlaps in subject matter with the instant genus, the absolute size of the genus is not correlative to a conclusion of obviousness. Also, the Examiner fails to point out where in the prior art the motivation exists to select the claimed species or subgenus.

Therefore, even though the Examiner states that the prior art teaches a small group of compounds within a genus that overlaps in subject matter with the instant genus, and it would have been obvious for one of ordinary skill in the art to easily envision and test the compounds that overlap with the prior art genus of compounds, these facts do not give rise to a prime facie case of obviousness. There still must be "some suggestion or motivation" to modify the prior art to

arrive at the new claimed invention, and such motivation must be found in the prior art, not the Applicant's specification.

In order to establish a *prime facie* case of obviousness, the Examiner must also show a reasonable expectation of success. It is well known that the pharmaceutical arts are highly unpredictable. The disclosure in Friebe et al. of compounds of Formula I as being useful for treatment of allergic diseases does not give rise to any presumption or reasonable expectation that the new claimed invention would be useful as PPAR delta activators, and useful for treating diseases or conditions such as dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, obesity, type 2 diabetes mellitus, type 1 diabetes, insulin resistance, hyperlipidemia, anorexia bulimia and anorexia nervosa. Thus, the Examiner has failed to establish a reasonable expectation of success as required by MPEP §2143.

For the reasons stated above, the Examiner has failed to point out where "some suggestion or motivation" exists in the references themselves or the knowledge generally available to one of ordinary skill in the art to modify the reference to arrive at the instant invention. Also, the Examiner has failed to demonstrate a reasonable expectation of success. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness, and the rejection is nothing more than improper hind-site construction of the Applicant's claimed invention. Applicants respectfully request withdrawal of the rejection.

The Office Action states claims 1-4, 6, 9, 10, and 17 are rejected under 35 USC 103(a) as being unpatentable over Grimova et al., because the prior art compound cited by the examiner and the instant invention are homologues of each other, and because it would have been obvious to one of ordinary skill in the art to synthesize homologues of the prior art compounds. Applicants respectfully traverse this rejection. The Applicants reiterate the arguments as stated above as they relate to homologues.

In order to establish a *prime facie* case of obviousness, the Examiner must also show a reasonable expectation of success. It is well known that the pharmaceutical arts are highly unpredictable. The disclosure in Grimova et al. of phenylacetic acid derivatives as being useful as anti-inflammatory agents does not give rise to any presumption or reasonable expectation that the new claimed invention would be useful as PPAR delta activators, and useful for treating diseases or conditions such as dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, obesity, type 2 diabetes mellitus, type 1 diabetes, insulin resistance, hyperlipidemia, anorexia bulimia and anorexia nervosa. Thus, the Examiner has failed to establish a reasonable expectation of success as required by MPEP §2143.

The Examiner has failed to point out where "some suggestion or motivation" exists in the references themselves or the knowledge generally available to one of ordinary skill in the art to modify the reference to arrive at the instant invention. Also, the Examiner has failed to demonstrate a reasonable expectation of success. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness, and the rejection is nothing more than improper hind-site construction of the Applicant's claimed invention. Applicants respectfully request withdrawal of the rejection.

The Office Action states claims 1-5, 10, and 17 are rejected under 35 USC 102(b) as being anticipated by Hcaplus 117:131082 contained in reference U. Applicants respectfully traverse this rejection. As stated in MPEP §2131.02, a species will anticipate a claim to a genus if the prior art discloses a species falling within the claimed genus. Hcaplus 117:131082 of reference U fails to fall within the Applicants claimed genus. Therefore, Applicants respectfully request withdrawal of the rejection.

Claim 17 is rejected as being indefinite. Applicants have amended claim 17. Applicants respectfully request withdrawal of the rejection.

PG4798USw

Applicants believe the present claims are in condition for allowance and such action is requested. Applicants believe that no fees are due in connection with the filing of this paper other than those specifically authorized herewith. However, should any other fees be deemed necessary to effect the timely filing of this paper, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 07-1392. If the examiner has any outstanding issues with the pending claims, she is encouraged to telephone the undersigned at (919)483-6334 for expeditious handling.

Respectfully submitted,

Jennifer L. Fox
Agent for Applicants
Registration No. 52,218

Date: 12 April 06

GlaxoSmithKline
Corporate Intellectual Property
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
Phone: 919-483-6334
Facsimile: 919-483-7988